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Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** _____
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DATA EVALUATION RECORD[1]

STUDY TYPE: Subchronic Inhalation Toxicity – Rat;
OPPTS 870.3465 [§82-4]; OECD 413.

PC CODE: 016331 **DP BARCODE:** D410187

TEST MATERIAL (PURITY): Momfluorothrin (95.7% a.i.)

SYNONYMS: S-1563

CITATION: Deguchi, Y. (2011) Four-week Repeated Inhalation Toxicity Study of S-1563 in rats. Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd, Osaka, Japan. Study #4218. October 25, 2011. MRID 49020012. Unpublished.

SPONSOR: Sumitomo Chemical Co., Ltd

EXECUTIVE SUMMARY:

In a subchronic inhalation toxicity study (MRID 49020012), momfluorothrin 95.7% a.i./Batch #9CM0109G) was administered to Sprague-Dawley rats (10/sex/concentration) by dynamic nose-only exposure at concentrations of 0, 0.050, 0.150, or 0.300 mg/L for 4 hours per day, 7 days/week for a total of 28 or 29 days. Observations on clinical signs, body weights, food consumption, ophthalmology, clinical chemistry, hematology, urinalysis, gross pathology and histopathology were conducted.

No treatment related effects were observed on mortality, body weights, food consumption, ophthalmology, hematology, urinalysis, gross pathology or histopathology.

Clinical signs were observed in male rats of the high dose group and included tremor after exposure on Day 1 and muscular rigidity before exposure on Day 3 in the same animal, ataxic gait before exposure on Day 2 in one animal, and hypersensitivity after exposure on Day 28 in one animal. Blood glucose levels were slightly but significantly decreased, and AST levels were significantly increased in high-dose males. Total cholesterol was significantly increased in high-dose females, and in mid- and high-dose males. Relative liver weights were significantly increased in male rats at all dose levels and in female rats at the mid- and high-dose. Absolute liver weights were increased in high-dose females. Significant increases in absolute and relative adrenal weights were observed in males at the low- and mid-dose and females at the high-dose.

1 Disclaimer: The attached Data Evaluation Record is a modified version of the Tier II Summary provided by Sumitomo Chemical Co. Ltd. Portions of this document may have been altered by the EPA reviewer.

Gait changes observed in 1 female rat each at 0.150 mg/L and 0.300 mg/L were not considered to be treatment related as they only occurred in 1 animal from each dose level and occurred prior to treatment on day 2. Liver effects observed at 0.150 mg/L were considered to be adaptive as no corroborating histopathological effects were observed and the decrease in AST enzyme is opposite of the biological response expected from a damaged liver. While the liver effects at 0.300 mg/L may also indicate an adaptive response, increased AST in male rats may be indicative of the beginning stages of liver damage and the toxicity database shows liver tumor development at higher doses in male rats.

Therefore, the LOAEL is set at 0.300 mg/L based on increased liver weights, AST, and cholesterol and clinical signs including tremors and muscular rigidity. The NOAEL is 0.150 mg/L.

This 28 day subchronic inhalation toxicity study in the rat is **Acceptable/Non-Guideline** and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413 in the rat." Please refer to the deficiency section for justification on study classification.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIAL AND METHODS

1. Test Material S-1563
Description: Pale yellow powder
Lot/Batch: Lot No.: 9CM0109G
Purity: Purity: 95.7%
Stability: Stable over the period: 95.7% pure on March 2, 2010, and 95.4% pure on March 2, 2011.

2. Vehicle None

3. Test Animals
Species Rat
Strain Crl:CD(SD)
Age 8 weeks (at time of administration)
Weight Males weight ranged from 263 – 326 g, females weight ranged from 197 – 246 g
Source Charles River Laboratories Japan, Inc. (Shiga, Japan)
Acclimation period 13 days
Diet solid food CRF-1, *ad libitum*
Water Filtered tap water was provided *ad libitum*; contaminant analysis performed
Housing Animals were housed in groups of two in suspended stainless steel cages with stainless steel-wired front and floor and with aluminum walls.
Environmental conditions
Temperature 22-26°C
Humidity 40-70%
Air change ≥10 air changes per hour
Photoperiod 12 hour light / dark cycle

B. STUDY DESIGN:

1. In life dates: 16 February – 10 June 2011

2. Animal assignment: Animals were assigned by body weight stratification using a random computer-generated algorithm to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Nominal conc. (mg/L)	Analytical conc. (mg/L)	MMAD µm	GSD	Rats/sex
Control	0	0	-	-	10
Low (LCT)	0.05	0.062	4.49	2.95	10
Mid (MCT)	0.150	0.170	5.00	2.57	10
High (HCT)	0.300	0.320	5.07	2.49	10

3. **Dose selection rationale:** The dose levels were selected based on the results from a 1-week inhalation study in which doses of up to 0.284 mg/L resulted in tip toe gait in 1 of 8 males, and 2 of 8 females, and tremors in 1 of 8 females.

4. **Generation of the test atmosphere / chamber description:**.

   Test atmosphere concentration: During the exposure, aerial concentration of the test substance was measured by gravimetric analysis and by chemical analysis for 4 to 5 times, respectively. Results are in table 1 above.

   Particle size determination: Particle size was measured twice a day, two times per week during the exposure period, and on the last day of exposure. A cascade impactor (Marple model 296, Nippon Thermo Co., Ltd., Kyoto) was connected to a sampling line, and 2.5 to 47 L of the dust aerosol in the chamber was drawn at the speed of 1 L/min into the impactor. The mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were calculated from the particle size distribution obtained from the measurement, using the Probit method. Results are in table 1 above.

5. **Statistics:** Body weight, body weight gain, food consumption, urinalysis (quantitative parameters), hematology tests, blood chemistry tests, organ weight, and organ weight relative to body weight were subjected to Bartlett's test for homogeneity, followed by Dunnett's multiple comparison between the air control group and S-1563 groups if homogeneous or by Steel's multiple comparison if non-homogeneous in a similar manner.

   Urinalysis results (semi-quantitative parameters) were subjected to Mann-Whitney's U-test between the air control group and S-1563 groups.

   Results of the ophthalmological examination were compared between the air control group and S-1563 groups using Fisher's exact method.

   Findings of necropsy and of histopathological examination without grading were subjected to Fisher's exact method, and findings of histopathological examination with grading were subjected to Mann-Whitney's U-test, for comparison between the air control group and S-1563 groups.

   All tests were performed 2-sided except for Fisher's exact test of the results of ophthalmological examination which was performed 1-sided. The significance level was set at 5% and 1%.

   No statistical test was performed on clinical signs.

C. METHODS:

1. **Observations:**

   1a. Cageside observations: During the exposure period, all animals were observed every day before and during exposure (at 1, 2, 3, and 4 hours after the start of exposure), and at 1 hour after exposure.

1b. Clinical examinations: Animals were observed daily 1 hour after exposure. Prior to necropsy, animals were observed for findings the day after their last exposure.

2. **Body weight:** During the exposure period, all animals were weighed twice weekly. On the day of necropsy, all animals were weighed for final body weight before necropsy. Body weight gain was calculated by subtracting the previous weight from the current weight.

3. **Food consumption:** During the exposure period, the amount of food consumption was measured once weekly. Food consumption during approximately 48 continuous hours was measured for each cage, from which daily food consumption per animal was calculated.

4. **Ophthalmoscopic examination:** Six males and six females of the air control group and highest dose group had both eyes examined before and after mydriasis at week 4 of exposure under a binocular indirect ophthalmoscope. The mydriatic agent used was Mydrin-P. Since no effect was observed either in males or in females of the highest dose group, no ophthalmological examination was performed on animals exposed to 150 or 50 mg/m^3.

5. **Hematology and clinical chemistry:** All animals scheduled for necropsy were fasted for approximately 16 hours, after which they were euthanized by drawing blood from the abdominal aorta under isoflurane anesthesia. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*		Reticulocyte count
X	Blood clotting measurements*		
X	(Thromboplastin time)		
X	(Clotting time)		
X	(Prothrombin time)		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

b. Clinical chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
X	**ENZYMES** (more than 2 hepatic enzymes eg., *)	X	Total bilirubin
X	Alkaline phosphatase*	X	Total serum protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
X	Creatine phosphokinase		Serum protein electrophoresis
X	Lactic acid dehydrogenase (LDH)	X	Phoshoplipids
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		

	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

6. **Urinalysis**: Urine samples were collected from six males and six females in each group in Week 4. Samples were collected by forced urination and the CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	X	Blood / blood cells*
	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

* Optional for inhalation toxicity studies

7. **Sacrifice and pathology:** All animals were subjected to necropsy. The scheduled necropsies were performed after completion of treatment. Each animal was euthanized by drawing blood from the abdominal aorta under isoflurane anesthesia. A full macroscopic examination was performed and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM
X	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver*+
	Gall bladder* (not rat)
X	Bile duct* (rat)
X	Pancreas*
X	**RESPIRATORY**
X	Trachea*
XX	Lung*
X	Nose*
X	Pharynx*
X	Larynx*

X	CARDIOVASC./HEMAT.
X	Aorta, thoracic*
XX	Heart*+
X	Bone marrow*
X	Lymph nodes*
XX	Spleen*+
XX	Thymus*+
X	**UROGENITAL**
XX	Kidneys*+
X	Urinary bladder*
XX	Testes*+
XX	Epididymides*+
XX	Prostate*
X	Seminal vesicles*
XX	Ovaries*+
XX	Uterus*+
X	Mammary gland*

X	NEUROLOGIC
XX	Brain*+
X	Peripheral nerve*
X	Spinal cord (3 levels)*
XX	Pituitary*
X	Eyes (optic nerve)*
X	**GLANDULAR**
XX	Adrenal gland*+
X	Lacrimal gland
XX	Parathyroid*
XX	Thyroid*
X	**OTHER**
X	Bone (sternum and/or femur)
X	Skeletal muscle
X	Skin
X	All gross lesions and masses*

* Recommended for subchronic rodent studies based on Guideline 870.3465
+ Organ weights required

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** Clinical signs were observed in male rats of the high dose group and included tremor after exposure on Day 1 and muscular rigidity before exposure on Day 3 in the same animal, ataxic gait before exposure on Day 2 in one animal, and hypersensitivity after exposure on Day 28 in one animal. Tip toe gait was observed before exposure on Day 2 in one female each at 150 and 300 mg/m^3. Tip-toe gait was not considered to be treatment related as it occurred prior to dosing on day 2, in only one animal at each dose level, and was not observed in acute or subchronic neurotoxicity studies. In animals exposed to 150 and 300 mg/m^3, wet fur (head, face, ventral neck, thorax, abdomen, lumbar region, back, dorsal neck) was observed. The increase in the number of animals with wet fur was observed up to Day 13 in males and up to Day 15 in females, after which the increase was sporadically observed until the last day of exposure. Since neither salivation nor urinary incontinence were observed as clinical signs in the present study, the observed wet fur was considered not to be related to neurological symptoms.

   One animal treated at 50 mg/m^3 showed bleeding from the external genitalia before and after exposure on Day 24 and red urine before exposure on Day 25, these changes were judged to be unrelated to the test substance administration, since they were observed in 1 animal only in the low dose group.

   Other changes were judged to be unrelated to the test substance administration and are often observed in animals of this strain.

2. **Mortality:** No mortality was observed in either sex at any test concentration.

3. **Neurological evaluations:** Not conducted.

B. BODY WEIGHT AND WEIGHT GAIN: A slight non-significant decrease in body weight gain was observed in high-dose males. However, as no effects were observed on body weight this was not considered to be toxicologically relevant. No other treatment-related effects were observed.

TABLE 2. Average body weights and body weight gains [a]

Analytical concentration (mg/L)	Body weights (g±SD)				Total weight gain	
	Day 1	Day 8	Day 15	Day 27	g	% from control
Male						
0	298 ± 16.6	309 ± 17.2	324 ± 17.1	341 ± 17.7	43 ± 9.9	-
0.050	302 ± 17.9	315 ± 20.9	331 ± 23.0	347 ± 26.9	45 ± 14.9	+4
0.100	299 ± 13.2	308 ± 15.2	321 ± 17.7	340 ± 23.4	41 ± 13.2	-5
0.300	300 ± 20.3	307 ± 23.0	319 ± 26.6	334 ± 29.5	33 ± 13.6	-23
Female						
0	219 ± 10.8	230 ± 11.4	239 ± 14.2	243 ± 16.6	24 ± 7.9	-
0.050	221 ± 11.4	232 ± 12.1	237 ± 12.8	244 ± 16.4	23 ± 7.1	-4
0.100	222 ± 7.9	235 ± 10.5	243 ± 14.9	245 ± 15.7	23 ± 10.9	-4
0.300	223 ± 13.1	240 ± 11.8	250 ±15.4	251 ± 16.9	28 ± 9.9	+17

[a] Data obtained from pages 84-87 in the study report.
* Statistically different ($p < 0.05$) from the control.

** Statistically different (p <0.01) from the control.

C. FOOD CONSUMPTION:

1. **Food consumption:** No treatment-related changes were identified.

2. **Food efficiency**: Not evaluated

D. OPHTHALMOSCOPIC EXAMINATION: No treatment-related effects were detected.

E. BLOOD ANALYSES:

1. **Hematology:** A significant decrease in eosinophils was observed in males treated at 50 mg/m^3. However, changes were not dose-dependent and were considered not to be treatment-related. No other significant effects were observed.

2. **Clinical chemistry:** Blood glucose levels were slightly but significantly decreased, and AST levels were significantly increased in high-dose males. Total cholesterol was significantly increased in high-dose females, and in mid- and high-dose males. However, no dose-response was apparent in male rats. Decreased AST levels in female rats are opposite of the expected biological response resulting from a damaged liver and were not considered to be biologically relevant. Additionally, no histopathology or gross lesions were observed upon liver examination.

TABLE 3. Selected clinical chemistry parameters

Parameter	Dose level (mg/L)			
	0	0.050	0.150	0.300
Males				
Glucose	133 ± 9.5	130 ± 9.8	130 ± 7.5	117 ± 12.0** (-12%)
Total Cholesterol	47 ± 9.4	48 ± 6.9	57 ± 7.6* (+21.3%)	56 ± 6.1* (+19.1%)
AST	75 ± 9.9	76 ± 6.4	80 ± 9.1	103 ± 21.4** (+37.3%)
Females				
Total Cholesterol	53 ± 9.7	65 ± 8.0	67 ± 9.4*	68 ± 15.1** (+28.3%)
Phospholipids	104 ± 13.9	116 ± 14.3	123 ± 14.7* (+18.3%)	126 ± 20.9* (+21.2%)
AST	99 ± 39.0	84 ± 20.2	76 ± 7.0** (-23.2%)	82 ± 12.5 (-17.2%)

Data taken from pp.108-113 of the study report.
[a] Reported as Mean, with n=10 for all groups.
* Significantly different (p<0.05) from the control.
** Significantly different (p<0.01) from the control.
Numbers in parentheses equal percent change, relative to control value, calculated by reviewer.

F. URINALYSIS: No treatment related effects were observed on either sex. Females showed a slight but significant decrease in protein at the mid-dose. However, no dose response was observed and this effect was not considered to be treatment related.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Relative liver weights were significantly increased in male rats at all dose levels and in female rats at the mid- and high-dose. Absolute liver weights were increased in high-dose females. Significant increases in absolute and relative adrenal weights were observed in males at the low- and mid-dose and females at the high-dose. Adrenal weight changes in male rats were not dose-dependent, and there were no corroborating histopathological effects reported. Therefore, the changes were not considered to be biologically significant.

TABLE 4. Selected organ weights

Organ	Dose Level (mg/L)			
	0	0.050	0.100	0.300
Males				
Absolute weight (g)				
Liver	7.54 ± 0.561	8.31 ± 1.070	8.44 ± 0.806	8.31 ± 0.905
Adrenals	54 ± 6.7	64 ± 6.2* (+18.5%)	64 ± 10.1* (+18.5%)	59 ± 7.8
Relative to body weight (%)				
Liver	2.39 ± 0.094	2.57 ± 0.201* (+7.5%)	2.67 ± 0.176** (+11.7%)	2.69 ± 0.156** (+12.5%)
Adrenals	17.1 ± 2.52	19.7 ± 1.46* (15.2%)	20.4 ± 2.66* (+19.3%)	19.0 ± 2.81
Females				
Absolute weight (g)				
Liver	5.90 ± 0.513	6.04 ± 0.396	6.32 ± 0.567	6.85 ± 0.485** (+16.1%)
Adrenals	64 ± 7.6	69 ± 10.7	73 ± 8.2	77 ± 14.5* (+20.3%)
Relative to body weight (%)				
Liver	2.62 ± 0.195	2.69 ± 0.071	2.80 ± 0.160* (+6.9%)	2.93 ± 0.150** (+11.8%)
Adrenals	28.4 ± 3.02	30.4 ± 3.50	32.3 ± 4.04	33.0 ± 5.53* (+17.8%)

Data obtained from pages 114-121of the study report.
[1]Values are group means ± SD
Values in parentheses are percent differences from controls, calculated by the reviewer
*p < 0.05, ** p < 0.01

2. **Gross pathology:** No treatment-related effects were observed.

3. **Microscopic pathology:** No treatment-related effects were observed.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The study authors concluded that, when male and female SD rats were exposed to S-1563 at the exposure levels of 0, 50, 150, and 300 mg/m^3 by inhalation for 4 weeks to investigate the subacute toxicity, wet fur and neurological symptoms were observed in males and females of the 150 and 300 mg/m^3 groups. In addition, effect on the liver was observed in males and females of the 300 mg/m^3 group and in females of the 150 mg/m^3 group. These results suggest that the no observed adverse effect level of S-1563 was 50 mg/m^3 (observed mean aerial concentration: 62.2 mg/m^3) in both males and females under the experimental conditions used in the present study.

B. REVIEWER COMMENTS: Gait changes observed in 1 female rat each at 0.150 mg/L and

0.300 mg/L were not considered to be treatment related as they only occurred in 1 animal from each dose level, and occurred prior to treatment on day 2. Liver effects observed at 0.150 mg/L were considered to be adaptive as no corroborating histopathological effects were observed and the decrease in AST enzyme is opposite of the biological response expected from a damaged liver. While the liver effects at 0.300 mg/L may also indicate an adaptive response, increased AST in male rats may be indicative of the beginning stages of liver damage and the toxicity database shows liver tumor development at higher doses in male rats.

Therefore, the LOAEL is set at 0.300 mg/L based on increased liver weights, AST, and cholesterol and clinical signs including tremors are muscular rigidity. The NOAEL is 0.150 mg/L.

C. STUDY DEFICIENCIES: The MMAD was outside of the 1.00 to 3.00 µm range specified by the sub-chronic OCSPP guideline. Additionally, animals were dosed for 4 hours/day instead of the 6 hours/day specified by OPPTS Guideline 870.3465. However, minimal effects were observed at the top dose of 0.300 mg/L and the toxicity database does not support significantly increased toxicity from longer exposure durations. While a longer daily exposure may result in a more clearly defined adverse effect level at 0.300 mg/L, it is not expected that a lower LOAEL would occur. Therefore, this study is considered to be acceptable for risk assessment and classified as non-guideline.

Additionally, the following clarification was sent by the registrant:

"The test substance was micronized by a pulverizing mill before use in this study. Attempts were made to reduce the particle size of the test substance by modification of the temperature (the test substance was cooled with dry ice before micronization and added into the mill with dry-ice), pressure and duration of micronization. However, the MMADs immediately after micronization were over 3µm (3.121 to 3.849 µm).

In general, MMADs during exposure are larger than that just after micronization owing to the influence of van der Waals force, adsorption and static electricity, all of which contribute to particle aggregation1),2). Therefore it is extremely difficult to keep the MMADs below 3µm during the exposure part of a study. The particle size of the test substance immediately after micronization was probably at the lower limit achievable by a pulverizing mill, but they still exceeded the recommended MMADs."